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TOXICOLOGY OF SOME FLUORO-ORGANIC COMPOUNDS

by

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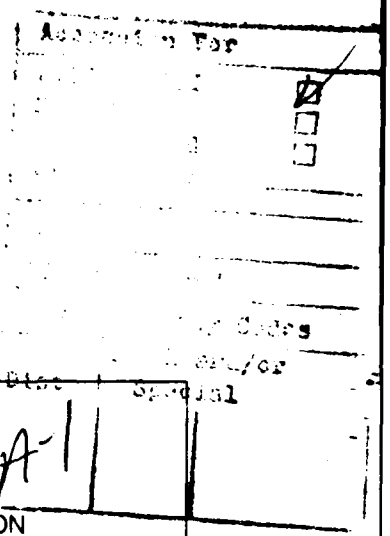

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А а	*А а*	A, a	Р р	*Р р*	R, r
Б б	*Б б*	B, b	С с	*С с*	S, s
В в	*В в*	V, v	Т т	*Т т*	T, t
Г г	*Г г*	G, g	У у	*У у*	U, u
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И и	*И и*	I, i	Ш ш	*Ш ш*	Sh, sh
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К к	*К к*	K, k	Ъ ъ	*Ъ ъ*	"
Л л	*Л л*	L, l	Ы ы	*Ы ы*	Y, y
М м	*М м*	M, m	Ь ь	*Ь ь*	'
Н н	*Н н*	N, n	Э э	*Э э*	E, e
О о	*О о*	O, o	Ю ю	*Ю ю*	Yu, yu
П п	*П п*	P, p	Я я	*Я я*	Ya, ya

*ye initially, after vowels, and after ъ, ь; e elsewhere.
When written as ё in Russian, transliterate as yё or ё.

RUSSIAN AND ENGLISH TRIGONOMETRIC FUNCTIONS

Russian	English	Russian	English	Russian	English
sin	sin	sh	sinh	arc sh	$\sinh^{-1}$
cos	cos	ch	cosh	arc ch	$\cosh^{-1}$
tg	tan	th	tanh	arc th	$\tanh^{-1}$
ctg	cot	cth	coth	arc cth	$\coth^{-1}$
sec	sec	sch	sech	arc sch	sech^{-1}
cosec	csc	csch	csch	arc csch	csch^{-1}

Russian	English
rot	curl
lg	log

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TOXICOLOGY OF SOME FLUORO-ORGANIC COMPOUNDS

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Submitted 14 June 1960

Fluorocompounds of ethylene represent an extremely promising raw material for the polymerization plastics industry. The unique polymerization properties of fluoro-olefins provide a new group of plastics - fluoroplastics - whose economic significance can hardly be exaggerated (D.D. Chegodayev, 1956).

There exists the belief among some that the toxicity of fluorohydrocarbons depends on the number of hydrogen atoms replaced by fluorine. According to this view, fluorine-saturation of the organic molecule leads to a reduction in its biological activity (~~Miller, 1949~~). This is why tetrafluoroethylene, in which four hydrogen atoms are replaced by fluorine, is considered to be a nontoxic or low-toxicity compound (~~Taylor, 1950~~; ~~Henne and Ladd, 1950~~; I.L. Knunynts and A.V. Fokin, 1951). However, one need only compare the concentrations of vinyl fluoride, vinylidene fluoride, tetrafluoroethylene and hexafluoropropylene required to produce a toxic effect in white rats - to question the correctness of this view (~~Table~~ 1).

Such comparison shows us that tetrafluoroethylene and hexafluoropropylene are more toxic than the other, less fluorine-saturated, compounds. Trifluoromonochloroethylene has even higher toxicity. M.M. Kochanov (1958) observed a 100% mortality in test rats at a trifluoromonochloroethylene concentration of 36 mg/l. This high toxic-

ity can apparently be explained by the chlorine in the fluoro-olefin molecule.

Under industrial conditions the toxic properties of fluoro-olefins result from the use of technical products which contain extremely toxic impurities - impurities which are not only unnecessary but often even harmful to the technological process. It is these impurities which predetermine the specific toxic effect of the technical product. In one study on the toxicity of vinylidene fluoride, its absolute lethal concentration for white rats and mice was determined at 2 mg/l, while for 10 other specimens of the compound concentrations as high as 80 vol. % (2096 mg/l) had no visible effect on test mice, which, in fact, survived. Our own studies showed that specimens of hexafluoropropylene of varying degrees of purity differed greatly from one another with respect to toxicity. The absolute lethal concentration for white rats for 4 specimens of hexafluoropropylene proved to be 20, 45, 60, and 82.5 mg/l.

We can assume, therefore, that the toxicity of hexafluoropropylene is related to the presence in this compound of impurities, particularly perfluoroisobutylene. This prompted us to study the toxicity of relatively pure perfluoroisobutylene and the same compound in a mixture with perfluorobutenes. We also studied perfluorobutenes which were practically free of perfluorobutylene (Table 2). Practically pure perfluoroisobutylene in a concentration of 0.015 mg/l resulted in the mortality of all test animals, while the technical product, which contains approximately 41% perfluoroisobutylene, produced the same toxic effect only in a concentration of 0.035 mg/l. When white rats inhaled perfluorobutenes purified of perfluoroisobutylene, no lethal outcomes were observed - even at a concentration of 40 mg/l.

The great danger imposed by perfluoroisobutylene is suggested by the very narrow range between its maximal tolerable and absolute lethal concentrations, which in our study was 0.0025-0.005 mg/l for white rats and 0.01-0.025 mg/l for white mice. Finally, In experiments with perfluoroisobutylene, we were unable to establish a minimal lethal

concentration for white rats, since the test animals which had been poisoned either all died or all lived.

Pathological studies revealed that perfluoroisobutylene poisoning is characterized by acute vascular disorders of the internal organs, morphologically manifested as acute hyperemia and hemorrhages in the lungs and kidneys. Vascular disturbances in the lungs (acute hemorrhage) (Fig. 1)_ were particularly marked. Another salient feature was the state of the bronchial epithelium, whose cells acquired the compacted appearance usually associated with chemical burns. Additional evidence of the chemical nature of the injury was leukocyte infiltration of the bronchial walls and peribronchial tissues. Perfluoroisobutylene also appears to have an irritating effect on the hematopoietic system. Evidence of this is the marked giant-cell reaction and slight decline in lymphocytes of the spleen. In the kidneys marked dystrophic changes - albuminoid, granular degeneration with cell plasmolysis (Fig. 2) were primarily observed. Albuminoid granular degeneration, and sometimes also fatty degeneration, were noted in the liver as well.

Autopsy materials and pathological studies of test animals which had succumbed to acute hexafluoropropylene poisoning show that, just as in the case of perfluoroisobutylene poisoning, primary injuries are characterized by severe vascular disturbances (overfilling and widespread hemorrhaging), edema, and emphysema of the lungs, dystrophic changes in the liver and kidneys, right up to necrosis of the epithelium of the convoluted renal tubules, hemolysis of erythrocytes, and degeneration of lymphocytes. Such changes were also revealed in acute tetrafluoroethylene and trifluoromonochloroethylene poisonings [A.I. Zhemerdey (1958) and M.M. Kochanov (1958)].

Thus, in their acute manifestation, fluoro-olefins present an identical pattern of injury, in which their degree of expression is dependent on the nature and quantity of impurities in the main product. The toxicity of fluoro-olefins is greatly increased by

perfluoroisobutylene, small quantities of which are especially dangerous. Comparison of the toxicity of perfluoroisobutylene with that of certain other compounds reveals (Table 3) that perfluoroisobutylene is more toxic than phosgene, ketene, nitric oxides, hydrogen phosphide and hydrogen cyanide (based on lethal concentration index for white rats).

With repeated acute hexafluoropropylene and vinylidene fluoride poisonings and with chronic exposure to tetrafluoroethylene (A.I. Zhemerdey, 1957) and trifluoromonochloroethylene (M.M. Kochanov, 1958) test animals displayed a failure to gain weight, an increased oxygen requirement, change in peripheral blood, and pathohistological changes in their internal organs.

Animals poisoned by tetrafluoroethylene and trifluoromonochloroethylene experienced a decline in carbohydrate reserves and the subsequent development of functional hepatic insufficiency. This is indicated by a decline in blood sugar and by the nature of its surge after corresponding loading during tetrafluoroethylene and trifluoromonochloroethylene poisoning (A.I. Zhemerdey, M.M. Kochanov) and by the change in blood phosphatase activity, which, in chronic exposure to trifluoromonochloroethylene, decreased by 35-85% and by 21-45% in experiments with tetrafluoroethylene.

The specific effect of fluorinated olefins, revealed in acute, chronic, and repeated acute tests, depends on both the degree of purity of the monomers and on chemical conversions which may occur when monomers of fluoro-olefins enter a living organism.

Chemical reactions characteristic of fluoro-olefins give us some idea about the mechanisms by which fluorinated olefins exert their biological effect. Even at a normal ambient air temperature and atmospheric pressure, fluoro-olefins have specific reactions accompanied by the formation of peroxide compounds. These compounds then decompose and undergo hydrolysis, which may in turn lead to the formation of

extremely toxic substances - fluorophosgene and hydrogen fluoride. For example, the oxidation of trifluoromonochloroethylene may result not only in the formation of fluorophosgene and hydrogen fluoride, but in the formation of oxalic acid and hydrogen chloride as well.

We can assume that identical chemical reactions may also occur when fluoro-olefins find their way into the human body.

The pathohistological changes in the internal organs which are revealed in fluoro-olefin poisoning may be explained by the effect of the fluorophosgene, hydrogen fluoride, and oxalic acid which form in the body through chemical conversion.

A very important problem from the hygienic standpoint is the decomposition of fluoroplastics at the high temperatures which are required in the treatment of plastics. When teflon is heated to even 204° solid and gas decomposition products are produced, which, in addition to tetrafluoroethylene, may contain hexafluoropropylene, octafluorocyclobutane, and perfluoroisobutylene (Troyanskiy et al., 1959). Moreover, during depolymerization and pyrolysis of fluroplastic-3 and fluroplastic-4, fluorophosgene, fluorochlorophosgene, hydrogen fluoride, hydrogen chloride, and a number of other volatile, low-molecular saturated and unsaturated fluoro-organic compounds may be liberated (Ye.A. Peregud, B.S. Boykin, 1958; M.M. Kochanov, 1958).

The picture produced by poisoning with the decomposition products of fluoroplastic-4 and fluoroplastic-3 in experiments is characterized by irritation of the mucuous membranes of the upper respiratory tract and the eyes.

Pathoanatomical and pathohistological studies show that the death of animals after inhalation of pyrolysis products of fluoroplastics occurs with manifestations of increasing edema and emphysema of the lungs.

The pathology which is observed when the products of thermal decomposition of fluoroplastics are inhaled is reminiscent of the pattern of injuries observed in poisoning by pefluoroisobutylene and other fluoro-olefins.

Conclusion

1. The current belief that fluoro-olefins in industrial situations are harmless is not well-founded and is misleading from the health safety standpoint. The products formed from the decomposition of polymerization plastics based on such compounds are undoubtedly toxic.

2. The toxicity of fluorinated olefins under industrial conditions is determined by their chemical activity, by their degree of purity, and by the possibility of formation of peroxide compounds followed by the decomposition and hydrolysis of these compounds. Substances formed in this way must be considered biologically aggressive.

3. Pathological changes in animals which have succumbed to acute poisoning by certain fluoro-olefins or the pyrolysis products of fluoroplastics are characterized by acute vascular disturbances (hyperemia, hemorrhage), edema, various degrees of emphysema of the lungs and degenerative changes in the kidneys and liver.

4. The concentration of potentially toxic impurities - particularly perfluorobutylene - must be regulated in fluoro-olefins which are used industrially.

Table 1. Toxicity of various fluoro-olefins

Key: 1 - compound; 2 - concentration (in mg/l); 3 - duration of exposure (in minutes); 4 - toxic effect; 5 - source; 6 - vinyl fluoride; 7 - slight narcosis; 8 - Lester and Greenberg (1950); 9 - vinylidene fluoride; 10 - indications of poisoning of the lung; 11 - Ibid.; 12 - trifluoromonochloroethylene; 13 - absolute lethal concentration; 14 - M.M. Kochanov (1958); 15 - Tetrafluoroethylene; 16 - Ibid.; 17 - A.I. Zhemerday (1958); 18 - hexafluoropropylene; 19 - authors' studies.

Footnote (1): Experiments conducted with specimens varying in degree of purity.

1 Вещество	2 Концентрация (в мг/л)	3 Продолжительность экспозиции (в минутах)	4 Токсический эффект	5 Источник
6 Фтористый винил	564,3–1128,6	30	Легкий наркоз 7	Лестер и Гринберг 8 (1950)
9 Фтористый винилиден	1048	30	10 Признаки легкого отравления	Они же 11
12 Трифторомонохлорэтилен	36	120	Абсолютная смертельная концентрация	М. М. Кочанов 14 (1958)
15 Тетрафторэтилен	102,3	120	16 То же 16	А. И. Жемердей 17 (1958)
18 Гексафторпропилен	20–82,5[1]	120	» »	Собственные исследования 19

Table 2. Maximal tolerable and lethal concentrations (mg/l) of perfluorobutylene and perfluorobutenes (2-hour exposure).

Key: 1 - compound; 2 - white rats; 3 - white mice; 4 - maximal tolerable; 5 - absolute lethal; 6 - minimal tolerable; 7 - perfluoroisobutylene (practically pure); 8 - perfluoroisobutylene (41% of compound); 9 - perfluorobutenes.

1 Вещество	2 Белые крысы		3 Белые мыши		
	4 максимальная переносимая	5 абсолютная смертельная	4 максимальная переносимая	6 минимальная смертельная	5 абсолютная смертельная
7 Перфторизобутилен (практически чистый)	0,0125	0,015	0,005	0,01	0,015
8 Перфторизобутилен (содержит 41% вещества)	0,03	0,035	0,01	0,03	0,035
9 Перфторбутены	10,0		20,0		40,0

Table 3. Lethal concentrations of perfluoroisobutylene and some other industrial compounds.

Key: 1 - perfluoroisobutylene; 2 - phosgene; 3 - hydrogen cyanide; 4 - hydrogen fluoride; 5 - nitric acids; 6 - carbon monoxide; 7 - ketene; 8 - compound; 9 - concentration (mg/l); 10 - duration of exposure (in minutes); 11 - source; 12 - authors' studies; 13 - Harmful Substances in Industry. Part II. Edited by N.V. Lazarev. GKhI. L., 1954. 14 - Ibid.; 15 - Yu.P. Frolov (1944); 16 - S.L. Danishevskiy (1949).

№ п.п	8 Вещество	9 Концентрация (в мг/л)	10 Продолжительность экспозиции (в минутах)	11 Источник
1	Перфторизобутилен	0,015	120	12 Собственные исследования
2	Фосген	0,08	30	13 «Вредные вещества в промышленности», ч. II. Под ред. Н. В. Лазарева. ГХИ Л., 1954
3	Цианистый водород	0,12	90	14 Там же
4	Фосфористый водород	0,14—0,28	240	» »
5	Окислы азота	0,8—0,9	25	» »
6	Окись углерода	4,1	60	15 Ю. П. Фролов (1944)
7	Кетен	0,2	120	16 С. Л. Данишевский (1949)

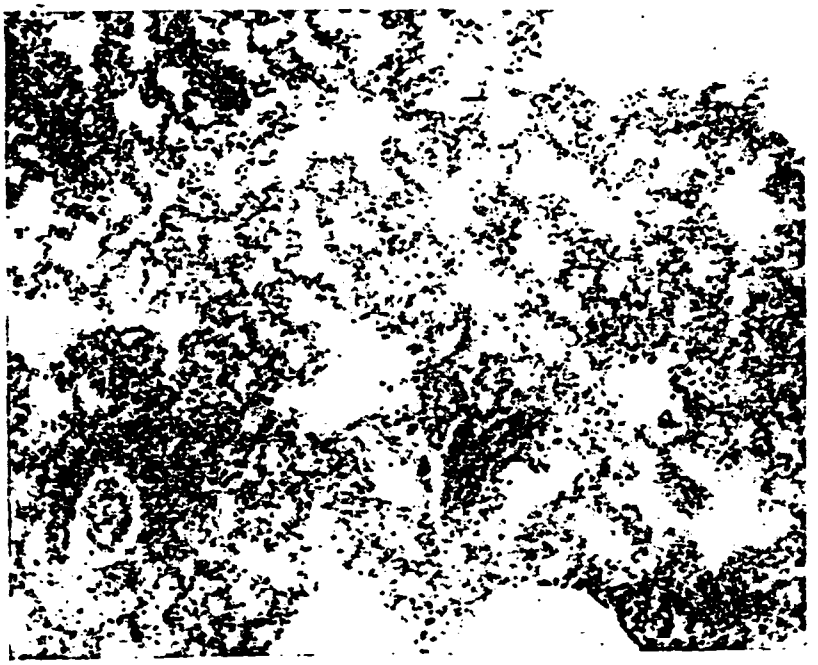

Fig. 1. Acute perfluoroisobutylene poisoning (white rat No. 760). Marked hyperemia of lung with edema and diapedetic hemorrhage.

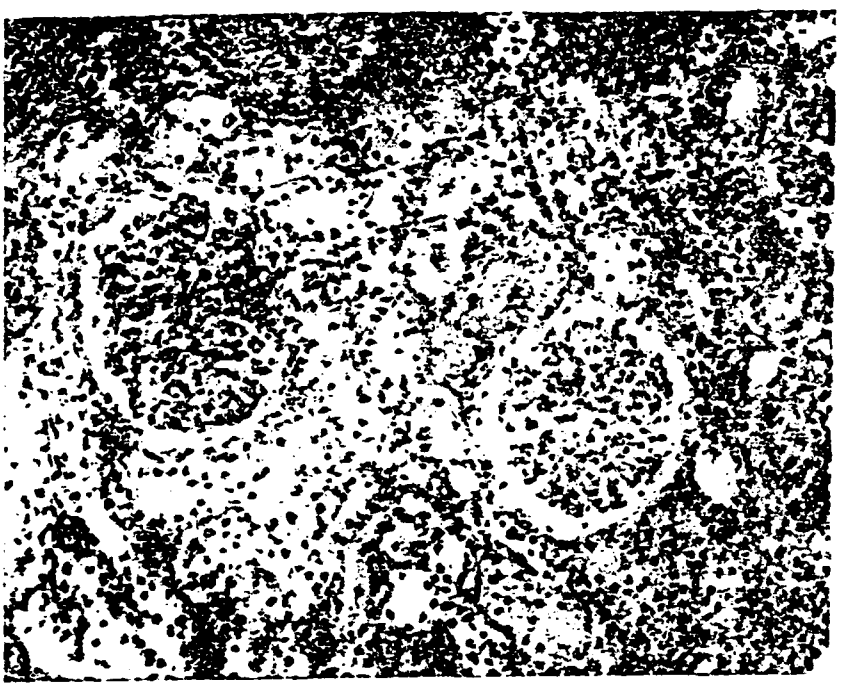

Fig. 2. Acute perfluoroisobutylene poisoning (white rat N. 760). Degenerative changes in epithelium of the convoluted tubules (plasmolysis, areas of necrosis).

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ON THE TOXICOLOGY OF SOME FLUORO-ORGANIC COMPOUNDS

S. L. Danishevsky, M. M. Koganov

Summary

A comparative study of toxic properties peculiar to some fluoro-organic compounds (monomers) shows them to possess low narcotic and distinctly pronounced specific action. Highly toxic are the products of thermal fluorolayers destruction.

The specificity of the fluorated olefines action, along with that of the products of thermal fluorolayers destruction is confirmed by the presence of an after-effect, as well as by the picture of pathohistological alterations in the internal organs, which, as a rule, is characterized by accentuated vascular disorders (hyperemia, hemorrhages), pulmonary edema and dystrophic hepatic and renal changes.

The toxicity of fluorated olefines is, apparently, determined both by their chemical activity and the extent of contamination with various impurities. Hypothetically, one may assume that the toxicity of these substances is also determined by the possible formation of peroxide compounds and their further hydrolysis, this resulting in the formation of highly toxic products.

The permissible level of contaminating admixtures in fluoro-olefines used in industry should be regulated from the viewpoint of occupational hygiene. This refers in the first place to perfluoroizobutylene, since even insignificant amounts of it imply great risks in handling the above products.

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